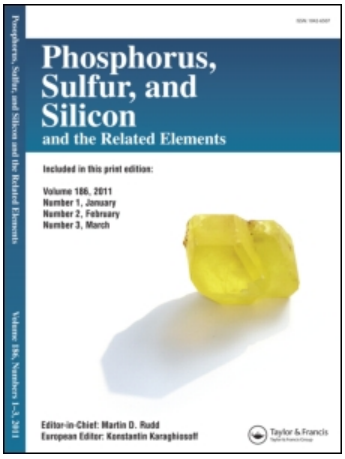

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Stereoselective Synthesis and Properties of Bay-Region Episulfides of Benzo[a]Pyrenes

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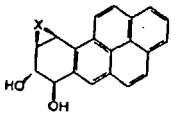
The bay-region diol episulfides of benzo[a]pyrene (BaP), DES- 1 (**1b**) and DES-2 (**2b**), were stereoselectively synthesized from the diol epoxides DE-2 (**2a**) and DE-1 (**1a**) respectively, apparently via the intermediacy of a five-membered 1,3-oxythiolane **4**. The DESs are thermodynamically unstable (desulfurization), but remarkably stable under hydrolytic conditions.

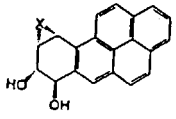
The bay-region diastereomeric diol epoxides **1a** (*DE-1*) and **2a** (*DE-2*) are the classic ultimate carcinogenic metabolites of the polycyclic aromatic hydrocarbons (PAH) as a consequence of their binding capability to DNA at its nuclephilic sites[1]. In view of (a) the higher polarizability and lower electronegativity of sulfur with its available d-orbitals, compared to that of oxygen; and (b) the ~10kcal less strain in episulfides than in epoxides, we have been intrigued by the possibility of replacing the epoxide oxygen in **1a** and **2a** with *sulfur*.[2] This would facilitate the evaluation of the anticipated different chemical and biological properties of the resulting diol episulfides **1b** and **2b** (DES-1 and DES-2). By analogy with the metabolically formed epoxides **1a** and **2a** both diastereomeric episulfides **1b** and **2b** are of interest.

Thus our highly efficient method that was developed for the conversion of epoxides to the corresponding episulfides, has been successfully applied within the polycyclic aromatic hydrocarbon epoxide series. Specifically, the highly stereoselective conversion of (+)-7β,8α-dihydrioxy-9β,10β-epoxy-7,8,9,10-tetrahydroBaP (DE-1, **1a**) and its diastereomeric 9,10-isomer (DE-2, **2a**) to the corresponding diol episulfides – **2b** (DES-2) and – **1b** (DES-1) – the sulfur analogs of their ultimately carcinogenic benzo[a]pyrene diol epoxide precursors, respectively, was achieved using excess of dimethylthioformamide (DMTF) in the presence of Lewis acid catalysts (e.g., $BF_3.Et_2O$) at low temperature.[3] By using the same method, the unsubstituted 9,10-epoxide of 7,8,9,10-tetrahydrobenzo[a]pyrene (BaP) was converted to the corresponding episulfide in over 90% yield.[3,4] All spectral data (UV, nmr and ms) were in accord with the assigned structures of the resulting episulfides.[4]



X = O: DE-1: 1a

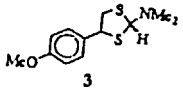
X = S: DES-1: 1b



X = O: DE-2: 2a

X = S: DES-2: 2b

Based on the isolation and characterization of diastereomeric mixtures of 1,3-dithiolanes in the Lewis acid-catalyzed reaction of 4-methoxystyrene oxide (yielding **3a,b**) and the unsubstituted BaP with excess of DMTF and prolonged reaction time,[1] and previously established mechanistic patterns,[2,5] the intermediacy of the five-membered 1,3-oxythiolanes **4** are invoked in these Des to DESs stereoselective transformations.



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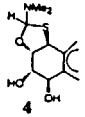

4

The properties of DES-1,2 derived from DE-2,1 respectively, were studied further.[1] Thus, for example, in neutral, 10% dioxane: water at rt DES-1 is thermally unstable and undergoes ~5-10% desulfurization to BaP 7,8-dihydrodiol overnight. A solid sample stored at -18°C for 1 yr was found to contain ~30% dihydrodiol. In contrast, this BaP DES is remarkably stable (at least 10^4 less reactive than BaP DE-2) toward aqueous acid (40% dioxane:water).[1] Studies in Chinese hamster V-79 cells indicated this BaP DES – in accord with its chemical properties and theoretical considerations – to have very low toxicity and mutagenicity compared to BaP DE-2.[1]

Further cancer research-related studies of the DESs and closely-related systems are currently underway at the authors labs and the full results will be published elsewhere in due time.

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